REMARKS

Without prejudice or disclaimer, claim 38 is amended. Claim 133 is added. Claims 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132 are reiterated. Claims 1-37, 39-40, 44, 47, 60, 63-64, 67-68, 72, 75, 87-88, 91-92, 94-115 and 125-130 were previously cancelled. Upon entry of this amendment, claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132-133 will be pending.

Support for the claim amendment and new claim can be found, *e.g.*, at least in Example II at page 48, Example III at page 51, last sentence; and Example VI, page 66, line 7. No new matter has been added.

The claim amendments made herein are for the purpose of expediting prosecution of the instant application. Applicants do not acquiesce to the rejections made by the Office, and reserve the right to pursue the canceled subject matter in one or more continuing applications.

Rejection of Claims 38, 41, 48, 49, 65 and 116 under 35 USC §102(b)

In paragraphs 4-5 of the Office Action, the Office has maintained the rejection of claims 38, 41, 48, 49, 65 and 116 under U.S.C. §102(b) as allegedly being anticipated by Liu *et al.* (*Biochemistry*, 1979, 18, 690-7). The Office states that:

> Because the structure of the insulin derivative taught by Liu et al. is identical to the claimed derivative, the prior of Liu *et al.* inherently meets this functional limitation. With respect to claim 116, the MB-insulin was purified in phosphate buffered saline which is a pharmaceutically acceptable carrier.

In maintaining the present rejection, the Office further asserts that:

> [T]he amended claims are not limited to insulin derivatives wherein the maleimido group is coupled to only the α-amino group of the N-terminus of the B chain. Rather, the claim is drawn to an insulin derivative **comprising** an insulin molecule and a maleimido-containing reactive group coupled to the α-amino group of the N-terminus of the B chain of the insulin molecule (emphasis added).
>
> Given this interpretation of "comprising", the amended claims state that the insulin derivative must have a maleimido-containing reactive group coupled to the α-amino group of the N-terminus of the B chain but do not exclude the possibility

> that the insulin derivative further includes a maleimido-containing reactive group coupled to other α-amino groups in the insulin molecule. Therefore, the MB-insulin taught by Liu *et al.* anticipates the claims and the rejection is maintained.

This rejection has been met by the amendment to claim 38, and claims 41, 48, 49, 65 and 116 dependent therefrom, to recite a purified insulin derivative that includes an insulin molecule and a single reactive group for covalently bonding an albumin, the reactive group being a maleimido-containing group that is coupled to an α-amino group of the N-terminus amino acid of the B chain of the insulin molecule. New claim 133 is directed to a pure fraction of an insulin derivative comprising an insulin molecule connected with or without a linker to a single maleimido-containing group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain, wherein the maleimido-containing group is coupled to an α amino group of the N-terminus amino acid of the B chain of the insulin molecule. Thus, the rejected claims are directed to either a purified form or a purified fraction of an insulin derivative having a single maleimido-containing reactive group reactive with only one of the several available amine groups, *i.e.*, coupled only to the α-amino group of the N-terminus of the B chain of the insulin molecule.

Liu *et al.* do not inherently anticipate the insulin derivative recited in the amended claims. Liu *et al.* disclose a reaction of *m*-maleidobenzyol-N-hydroxysucciminimide with insulin (*see* second column on page 691 of Liu *et al.*, *supra*). None of the amino groups of the insulin molecule used by Liu *et al.* appear to be protected, *e.g.*, Boc-protected, prior to the reaction of the *m*-maleidobenzyol-N-hydroxysucciminimide ester (MBS) with insulin. Thus, a mixture of insulin derivatives having one, two, three or more maleimido-containing group coupled to any one of the amino groups present in insulin (*e.g.*, coupled to one or more of A1, B1 or B29 residues of insulin), is formed. Liu *et al.* also disclose a desalting step through the Sephadex G-25 column that is expected to remove smaller molecular weight contaminants, thus still resulting in a mixture of insulin derivatives having one, two, three or more maleimido-containing groups coupled to different amino groups present in insulin. Therefore, the insulin derivatives in the mixture synthesized by the methods of Liu *et al.* are not a purified form

or a purified fraction of the insulin derivatives synthesized to contain only those coupled to the α-amino group of the N-terminus of the B chain of the insulin molecule, as presently claimed.

As provided in section 2112 of the Manual for Patent Examination Procedures (MPEP):

> To establish inherency, the extrinsic evidence 'must make it clear that the missing descriptive matter is necessarily present in the thing described in the reference' .... Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

As discussed above, the methods disclosed by Liu et al. do not result explicitly or inherently in a **purified form or purified fraction** of an insulin derivative containing a **single** maleimido-containing reactive group being coupled to the α amino group at the N-terminus of the B chain of an insulin molecule. Therefore, Liu *et al.* do not anticipate the claims as amended. Applicants respectfully request that the Office withdraw this rejection.

Rejection of Claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132 under 35 USC §103

In paragraphs 7-20 of the Office Action, claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Bridon *et al.* (WO 00/69900) in view of Jones *et al.* (WO 95/05187), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys et al. (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon et al. (CA 2363712) and Vajo *et al.* (*Endocrine Rev.*, 2001, 22, 706-717).

This rejection is traversed. The claims as currently pending are directed to a purified insulin derivative, or a purified fraction of an insulin derivative, comprising an insulin molecule and a single maleimido-containing group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain, wherein the maleimido-containing group is coupled to an α amino group of the N-terminus amino

acid of the B chain of the insulin molecule; albumin- containing conjugates thereof; methods of treating glycaemic-related diseases using the insulin derivatives and conjugates; pharmaceutical compositions thereof; and method of making the conjugates.

The present claims are directed to an insulin derivative having a selected site for coupling a single maleimido-containing group, *i.e.*, the α amino group of the N-terminus amino acid of the B chain of the insulin molecule. None of the references cited by the Office and discussed in Applicants' Amendment of April 15, 2009, alone or in combination, teaches or suggests modifying an insulin molecule by coupling the maleimido-containing group at the α amino group of the N-terminus amino acid of the B chain of the insulin molecule. Moreover, none of the references cited by the Office, alone or in combination, teaches or suggests that the claimed albumin conjugates of the insulin molecule would have a binding affinity to the insulin receptor at least 5 to over 50-fold greater than albumin conjugated via the maleimido-containing group to other available coupling positions of insulin.

The above cited references were extensively discussed in Applicants' April 15 Amendment, the substance of which is reiterated here.

More specifically, Bridon *et al.* (WO 00/69900) do not teach or suggest conjugation of albumin via a maleimido-containing reactive group to the N-terminal amino acid of the B chain over any of the other available polar groups of insulin, for example, the amino groups at A1, B1 or B29; or the carboxyl groups at the side chains of amino acid residues A4, A17, B13, B21 or the C-terminal residues of the insulin A or B chain. Neither Bridon *et al.* teach or suggest that conjugation to the B1-site of insulin would lead to significantly higher affinities than conjugation at other available coupling positions of insulin.

The secondary references, alone or in combination, fail to make up for the deficiencies in WO 00/69900. In particular, Bridon *et al.* (CA 2363712) disclose insulinotropic peptide derivatives containing a maleimino-group capable of forming a covalent bond with albumin, as well as conjugates thereof. The particular insulinotropic peptides disclosed in WO 00/69900 are GLP-1, exendin-3 and -4, which are short single chain peptides about 40 amino acids in length that bind and activate the GLP-1 receptor.

In contrast, insulin is a two chain large protein having a highly organized three dimensional structure with three disulfide bonds that binds to and is internalized by a completely different receptor, the insulin receptor. Based upon the differences in structure and function of insulinotrophic peptides and insulin, it would not have been obvious to one of ordinary skill to use the approach disclosed by Bridon *et al.* (CA 2363712) to produce the claimed insulin molecule. One of ordinary skill in the art would not have expected, based upon the teachings of Bridon et al. (CA 2363712), that insulin, a complex three-dimensional protein, covalently bound to a protein as large as albumin, would bind its receptor with sufficient affinity and be internalized into a cell such that the insulin would have an anti-diabetic effect.

Additional secondary references of Jones *et al.*, Jonassen *et al.* and Baudys *et al.* all disclose insulin linked to another moiety by a non-covalent bond and/or linked to another moiety at a position **other** than the N-terminus amino acid of the B chain of insulin. For example, Jonassen *et al.* disclose the use of fatty acids to **non-covalently** bind the **lysine at position 29** of the B chain of insulin to serum albumin. Jones *et al.* disclose use of thyroxine to **non-covalently** bind a blood protein to the N-terminal amino acid of the B chain of insulin. Baudys *et al.* disclose the covalent bonding of carboxymethyl dextan to the N-terminal amino acid of the **A chain of insulin**.

The Baudys *et al.* reference cited by the Office suggests attaching a moiety to insulin at either the N-terminal amino acid of the A chain of insulin or at the lysine at position 29 of the B chain of insulin. In contrast, Applicants have shown that albumin covalently bound to the N-terminal amino acid of the B chain of insulin results in an albumin conjugate that has a significantly better binding affinity for the insulin receptor than albumin covalently bound to insulin at other available positions.

Several of the secondary references cited by the Office disclose non-covalent association of insulin with a blood protein. Non-covalently bonded blood proteins are expected to disassociate from the insulin complex so that insulin only, and not the blood protein, is internalized. The internalized insulin (that is ***not*** attached to the blood protein) has the anti-diabetic effect. In contrast, the claimed insulin conjugates are **covalently** bound to albumin. Thus, the insulin and albumin of the claimed insulin conjugates must

be internalized with albumin attached for insulin to have its anti-diabetic effect. These two approaches are completely different. One of ordinary skill in the art following the disclosure of non-covalently associated insulin would **not** have had the requisite motivation, or a reasonable expectation, that the covalently bonded insulin to albumin would have had the binding affinity shown, let alone that B1-modified insulin conjugates would have had significantly greater affinity compared to other insulin conjugates.

In maintaining this rejection, the Office acknowledges that Applicants presented in the specification, particularly in Example IX, "data that convincingly shows that conjugation to the α-amino group of the N-terminus of the B-chain is superior to that at other positions in insulin." However, the Office takes the position that the previous submission filed 15 April 2009 did not "present data or evidence to suggest that this result was in fact unexpected." (Office Action, paragraph 18). To support this position the Office states that:

> ....In the instant case, Applicant is arguing that it is unexpected that conjugation at the N-terminal amino acid of the B chain of insulin would result in significantly better binding affinity to the insulin receptor as compared to conjugates having albumin attached via a maleimido-containing reactive group to either the N-terminal amino acid of the A chain or the lysine at position 29 at the B chain of the insulin molecule. However, a beneficial result is not necessarily an indication of non-obvious. MPEP § 716.02 states: "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) In order to determine if the results presented in Table 1 in the response filed 15 April 2009 are in fact unexpected, Applicant must support this assertion with factual evidence that the skilled artisan would have predicted a different result. Applicant does not supply such evidence in the response filed 15 April 2009. Although Applicant presents data that convincingly shows that conjugation to the α-amino group of the N-terminus of the B-chain is superior to that at other positions in insulin, it does not present data or evidence to suggest that this result was in fact unexpected.

Although the Office acknowledges that conjugation to the α-amino group of the N-terminus of the B-chain is superior to that at other positions in insulin, it concludes that no evidence has been presented that such superior effects were indeed unexpected. To support this position, the Office cites to two references: Uchio *et al.* ("Site-specific insulin conjugates with enhanced stability and extended action profile," *Advanced Drug*

Delivery Reviews, **1999**, 35, 289-306); and Hinds *et al.* ("Synthesis and Characterization of Poly(ethylene glycol)-Insulin Conjugates," *Bioconjugate Chem.* **2000**, 11, 195-201). Each of the grounds for this rejection is discussed in more detail below.

Applicants submit that, at the time the application was filed, there was no reasonable expectation that an insulin derivative having an albumin coupled at position B1 would result in an insulin-albumin conjugate having significantly improved receptor binding and activation activity of the insulin receptor. In fact, several reports had shown that acylation of the ε-amino group in the side chain of Lys^{B29} was a preferred target for modification with fatty acids. For example, Markussen, J. *et al.*[1] describe fatty acid acylated insulins in the ε-amino group of Lys^{B29}, such as Lys^{B29}-tetradecanoyl des-(B30) insulin. It is noted that the fatty acid substituent on residue B29 Lys binds non-covalently to circulating albumin protein *in vivo*. In fact, LEVEMIR®, long-acting basal insulin analogue of human insulin which is was approved by the FDA in June 2005, corresponds to Lys^{B29}-tetradecanoyl des-(B30) insulin, and thus has a C14 fatty acid chain coupled to the amino acid B29 in human insulin and has a deletion at the threonine residue in position B30. Thus, one of ordinary skill in the art reading Markussen would have been motivated to modify position B29 of insulin, instead of position B1.

In fact, Markussen *et al.* discourage modifying the insulin molecule at position B1 as follows:

> … [W]e knew that modifications of Phe^{B1} interfere with the formation of the insulin hexamer unit, which is the most desirable state due to its inherent stability [Ref. omitted]. Consequently, **acylation of the ε-amino group in the side-chain of Lys^{B29} became the preferred target for modification with fatty acids.** (Id. at page 282, right hand column, emphasis added).

Similarly, Whittingham, J.L. *et al.*[2] disclose the crystal structure of fatty acid acylated insulins in the ε-amino group of Lys^{B29}, and in particular, Lys^{B29}-tetradecanoyl des-(B30) insulin. This reference describes the end of the B chain, and in particular Lys^{B29}, as an "ideal position" for modification as follows:

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[1] Exhibit 1: Markussen, J. et al. (1996) *Diabetologia* 39:281-288, submitted herewith.

[2] Exhibit 2: Whittingham, J.L. et al. (1997) *Biochemistry* 36:2826-2831, submitted herewith.

> The fatty acid modification in NN304 insulin has been introduced in order to facilitate the temporary binding of insulin to circulating albumin. **The lipid has been placed in an ideal position at the end of the B chain, where it neither disrupts the aggregation properties of the molecule not abrogates its activity**, which is not different than that of human insulin [Ref. omitted]. *Id.* at 2830, right hand column (emphasis added).

Thus, based on the teachings of Markussen, J. *et al.* and Whittingham, J.L. *et al.* and the fact that commercially available insulin products like LEVEMIR® are modified at position B29, one of ordinary skill in the art would have selected position B29 as a site for coupling albumin to an insulin molecule, instead of position B1 as presently claimed.

The Office cites to two references: Uchio *et al. supra*; and Hinds *et al. supra*. to support the proposition that "the prior art reveals other instances wherein conjugation to this same position in insulin also resulted in superior properties." The Office concludes the characterization of these references by stating:

> Given that both Uchio *et al.* and Hinds *et al.* teach that conjugation to the α-amino group of the N-terminus of the B chain of insulin more significantly impacts stability of the insulin that conjugation to other sites, it would be expected that conjugation of albumin to the α-amino group of the N-terminus of the B chain of insulin would more significantly impact stability of the insulin that conjugation of albumin to other sites. Therefore, Applicant's results in Table 1 do not constitute unexpected results even if they do convincingly illustrate that conjugation to PheB1 is superior to conjugation to GlyA1 and LysB29. The beneficial results obtained for conjugation to the PheB1 site of insulin is expected rather than unexpected in light of the prior art of Uchio *et al.* and Hinds *et al.*

Applicants disagree with the Office's conclusion. Each of the references will be addressed individually below.

Uchio *et al.* disclosed insulin derivatives at positions GlyA1, PheB1 and/or LysB29 covalently modified with two different hydrophilic moieties, *i.e.*, carboxyl derivatives of monosaccharidic glycosides and methoxypolyethylene glycols of varying molecular weights. The Office takes issue of the finding described by Uchio *et al.* that:

> Only site-specific modification of PheB1 amino group with either moiety resulted in a pronounced increased resistance of insulin to fibrillation, indicating that the B-chain N-terminus of the insulin molecule is mechanistically involved in the fibrillation process. *Id.*, abstract.

The improved fibrillation of the modified insulin at the PheB1 amino group reported by Uchio *et al.* does not detract from the unexpected findings discussed above that an insulin-albumin conjugate having an albumin coupled at position B1 results in significantly improved receptor binding and receptor activation activity compared to insulin conjugates coupled at positions A1 and B29. Fibrillation is a measure of the denaturing and misfolding of insulin that leads to aggregation, and thus impacts the long-term stability of insulin. Thus, fibrillation is relevant to the long-term stability of insulin, and **not** to the binding to the insulin receptor or short-term biological properties of insulin.

Based on the data presented by Uchio *et al.*, one cannot reasonably reach a conclusion regarding the differences in insulin activity between a modification at the B1 site or the B29 site. For example, Table 1 at page 295 of Uchio *et al.* shows comparable biological activities among the mono-substituted SAPG-insulin derivatives modified at position GlyA1, LysB29 or PheB1 (*i.e.*, 22.2 $\pm$ 4.2; 24.2 $\pm$ 4.6; and 25.3 $\pm$ 5.1. IU/mg, respectively) (after short-term *in vivo* administration). Thus, based on this finding, one of ordinary skilled in the art would **not** have expected a dramatic effect in affinity or biological activity between B1-modified insulin, and either of A1- or B29-insulin. Di-substituted insulin, GlyA1-PheB1-$(SAPG)_2$-insulin showed slightly higher activities than mono-substituted insulin (*i.e.*, 28.9 $\pm$ 5.4), thus providing motivation to make insulin derivatives having more than one substituted site. It is noted that the present claims require the insulin derivatives to have a single maleimido-containing group.

Consistent with the results described above, Table 3 of Uchio *et al.* shows comparable biological activities after intravenous administration of mono-substituted pegylated-insulin derivatives at positions GlyA1, LysB29 and PheB1. In particular, GlyA1-PEG(600)-insulin, PheB1- PEG(600)-insulin and LysB29- PEG(600)-insulin showed similar biological activities, namely, 22.2 $\pm$ 4; 23.8 $\pm$ 4.2; and 25.0 $\pm$ 5.2 IU/mg, respectively. With respect to fibrillation activity, Table 3 only shows a comparison between GlyA1-PEG(600)-insulin and PheB1- PEG(600)-insulin, as the fibrillation data on LysB29- PEG(600)-insulin is not shown. This point is acknowledged by Uchio *et al.* where it is stated that:

> [W]e are synthesizing LysB29-PEG-insulin derivatives **which should also have more or less preserved bioactivity** [Ref. omitted] and **can serve as an alternative to Phe-B1-PEG insulins with regards to the protraction of insulin action**…..(Id. at page 302, emphasis)

As clearly stated above, the expectation articulated by Uchio *et al.* was that modifications at LysB29 would preserve bioactivity, while offering a more stable insulin alternative. Thus, no conclusive comparison of the activities of substitution at PheB1 and LysB29 was presented, but there was a clear expectation that a modification of LysB29 would have preserved bioactivity. In addition, it is noted that higher substituted forms of pegylated insulin (*e.g.*, GlyA1-PheB1-$(PEG(600))_2$-insulin and GlyA1-PheB1-LysB29$(PEG(600))_2$) showed a decrease in biological activity (*i.e.*, 19.2 ± 3.2), while resulting in a pronounced increase in resistance to fibrillation (*i.e.*, 26.4 ± 5.6 and 30.9 ± 5.3 days to fibrillation, respectively). Thus, biological activity seems to correlate inversely proportional to fibrillation activity at least for the higher substituted insulin molecules, *i.e.*, as the number of substituents increase the fibrillation activity increases, but the biological activity of insulin is reduced.

Lastly, the present claims require the insulin derivative to be coupled to albumin, thereby forming an insulin-albumin conjugate. A comparison of three different pegylated form of PheB1-insulin, PEG(600), PEG(2000) and PEG(5000) shows a trend of reduction of biological activity of the modified insulins (with a concomitant increase in resistance to fibrillation) as the molecular weight of the pegylated group is increased (see bottom three measures shown in Table 3). The decreased in activity as the molecular weight of the PEG group is increased is also seen in Table 4 where a 6-8 fold reduction in biological activity was seen as the size of the PheB1-PEG was increased from 600 D to 2 kD in the two mouse models tested. Thus, one would have expected that increasing the molecular weight of the attached group would lead to decrease biological activity since having a bulkier group covalently bonded to PheB1 would sterically affect the insulin-receptor binding and internalization. Albumin has a molecular weight of about 66 kDa and is a much larger molecule than the PEG groups tested by Uchio *et al.* (maximum

molecular weight of 5K). Albumin-insulin conjugate would have been expected to have a greater reduction in biological activity than that observed using the PEG(5000).

The second reference cited by the Office supports a similar conclusion as discussed above. Hinds *et al.* describe pegylated versions of insulin modified at either position B1 or B29. As before, modification of at position PheB1 seems to provide increased long term stability of the insulin molecule as detected by resistance to fibrillation, but as discussed above, the increased stability may not necessarily correlate with increased biological activity. This difference in activity is clearly observed in Table 4 on page 200 of Hinds *et al.* Increased size of the PEG group from PEG750 to PEG2000 led to an increase in stability of the higher pegylated form of insulin, while showing a 15% decrease in its biological activity. Albumin has a much higher molecular weight than PEG2000, and thus the skilled artisan would have expected a greater reduction in biological activity.

In sum, one of ordinary skill in the art would not have expected that conjugation of albumin to insulin via a maleimido-containing reactive group at the N-terminus amino acid of the B-chain would have resulted in an insulin-albumin conjugate that binds to and activates the insulin receptor with an affinity 5 to over fifty fold greater than albumin conjugated via a maleimido-containing group to other available positions of insulin. Furthermore, it was not predictable that insulin, a complex three dimensional protein, covalently bound with a protein as large as albumin, would bind its receptor with sufficient affinity and be internalized into a cell such that the insulin would have an anti-diabetic effect.

For at least the reasons provided above, the claims are patentable over the references cited by the Office. Applicants respectfully request that the Office withdraw this rejection.

Claim Rejections for Nonstatutory Obviousness-Type Double Patenting

In paragraphs 21-40 of the Office Action, the Office has rejected the pending claims on the grounds of obviousness-type double patenting.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s), because the examined application claim is either anticipated by or would have been obvious over the cited references. See, *e.g., In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). See also MPEP 804(II)(B)(1)(a).

Rejection of claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69, 71, 73-86, 89, 90, 93, 116, 117, 131 and 132 for nonstatutory obviousness-type double patenting as being unpatentable over claim 25 of U.S. Patent No. 7,307,148 (Application No. 11/112,277 which issued as a patent since the mailing of the previous Office Action). The Office states that claim 25 of U.S. 7,307,148 "recites insulin derivatives comprising an insulin molecule and a reactive maleimido-containing group for covalently bonding a blood protein, and conjugates of said insulin derivatives and the blood protein albumin."

This rejection is respectfully traversed. The pending claims are not obvious in view of the claims of the '148 patent. The claims as currently pending are directed to a purified insulin derivative, or a purified fraction of an insulin derivative, comprising an insulin molecule and a single maleimido-containing group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain, wherein the maleimido-containing group is coupled to an α amino group of the N-terminus amino acid of the B chain of the insulin molecule; albumin- containing conjugates thereof; methods of treating glycaemic-related diseases using the insulin derivatives and conjugates; pharmaceutical compositions thereof; and method of making the conjugates.

The claims as issued in the '148 patent are directed to chromatographic methods for separating albumin conjugates from unconjugated albumin, comprising the steps of loading the a solution containing the mixture onto a hydrophobic interaction chromatography matrix equilibrated under certain conditions; applying to said matrixa

gradient of decreasing salt concentrations; and collected the albumin conjugate. Claim 25 lists various insulin derivatives as possible conjugates that can be purified.

It is respectfully submitted that the present insulin derivatives claimed are patentably distinct over the chromatographic methods claimed in the '148 patent. The '148 patent claims one possible method of purifying insulin conjugates from unconjugated albumin. In fact, the purification method claimed in the '148 patent has no bearing on the insulin derivative claims (*e.g.*, claims 38, 41-43, 45, 46, 48-59, 61, 62, 65), as no albumin purification step is necessary in making the insulin derivatives. The recitation of certain insulin conjugates that can be purified using the chromatographic methods claimed in the '148 patent does not in any way render obvious the claims directed to the particular compositions of insulin derivatives and conjugates claimed in the present application.

Applicants also traverse the rejection of claim 42 on similar grounds over the '148 patent in view of Vajo et al. (2001) *Endocrine* Rev. 22: 706-717). Claim 42 is directed to a purified insulin derivative comprising an insulin molecule (chosen from insulin glargine, insulin detemir, insulin lispro, insulin aspart or insulin glulisine), and a single maleimido-containing group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain, wherein the maleimido-containing group is coupled to an α amino group of the N-terminus amino acid of the B chain of the insulin molecule. Vajos *et al.* merely disclose the use of native insulin and the insulin analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes. The present insulin derivatives claimed are patentably distinct over the chromatographic methods claimed in the '148 patent. The purification method claimed in the '148 patent has no bearing on the insulin derivative claims (*e.g.*, claims 38, 41-43, 45, 46, 48-59, 61, 62, 65), as no albumin purification step is necessary in making the insulin derivatives.

Reconsideration and withdrawal of this rejection is respectfully requested.

In paragraphs 24-39 of the Office Action, the Office has provisionally rejected the pending claims on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over:

(i) Claim 44 of copending application 11/981,474;

(ii) Claims 26-49 of copending application 11/982,033, in view of Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008), Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen et al. (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.,* **2001**, 22, 706-717); and

(iii) Claims 1-58 of copending application 11/645,297, in view of Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008), Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen et al. (citation No. 9, on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006) Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.,* **2001**, 22, 706-717).

Since the allegedly conflicting claims are pending in the present application and the copending application cited by the Office, Applicants defer addressing this rejection until either of the claims are indicated otherwise allowable.

CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. A Petition for an RCE, and an extension of time and appropriate fee are submitted herewith. Please charge any additional payments, or credit any overpayments, of the same to Deposit Account No. 50-2762, referencing Attorney Docket No. C2077-7016US.

Respectfully submitted,

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